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The Current Use of Studies on Promoters and Cocarcinogens in Quantitative Risk Assessment

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Several of the priority pollutants discussed in EPA's Ambient Water Quality Criteria documents have been reported to have promotion or cocarcinogenic activity. For example, phenol appears to have tumor-promoting activity in mice when repeatedly applied after initiation with either 7,12-dimethyl-1,2-benzanthracene (DMBA) or benzo(a)pyrene (BaP). Similarly, it has been reported that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is a potent promoter of liver tumors as well as a cocarcinogen. However, in developing guidelines to derive ambient water quality criteria, it became apparent that satisfactory approaches had not been developed for using promotion/cocarcinogen data in human health risk estimation, nor were available promotion and/or cocarcinogen data on individual chemicals strong enough to permit a defensible quantitative risk estimation, if such approaches had existed. For this reason, the criteria derived for pollutants with reported promotion/cocarcinogenic activities were based on approaches for carcinogenic (e.g., TCDD), toxic (e.g., fluoranthene) or organoleptic effects (e.g., 2,4-dichlorophenol).

Nonetheless, with advances in studies on both the biological mechanisms and dose/response patterns of promoters and cocarcinogens, it may be possible to develop a scientifically valid quantitative approach to use this type of data for derivation of ambient water quality criteria or other risk assessments. Some progress toward this goal and the problems associated with this effort are discussed.

Introduction

Of the 4 million chemicals present in the environment (*1*), more than 60,000 have been produced by industry in the last two decades, and 500 to 700 new compounds are added every year (*2*). Contamination of surface water by these compounds results from industrial or municipal discharges, accidental spillage during transportation, and other point or nonpoint sources. Migration of these chemicals through the soil from municipal land dump sites or other sources results in contamination of underground water.

A large number of these chemicals are toxic to human health and many are confirmed or suspected carcinogens. Since these contaminants occur in very low concentrations in the parts per billion or trillion range, a large percentage of the population is exposed to low doses over a long period of time. Several reports indicate that a direct relationship exists between increased incidence of cancer and the use of water from certain rivers in the U.S. (*3-10*). Exposure to these water pollutants does not only occur from drinking contaminated water but also from consumption of fish from these contaminated sources. Accordingly, our society has become increasingly conscious of the presence of these chemical contaminants in the environment.

Under the Clean Water Act, the U.S. Environmental Protection Agency (U.S. EPA) is required to develop an approach for controlling the release of hazardous pollutants in water. As part of this effort, the Environmental Criteria and Assessment Office (ECAO) in Cincinnati, with the support of the Carcinogen Assessment Group (CAG) in the Office of Health and Environmental Assessment (OHEA) was

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assigned the task of assessing the potential health risks associated with contamination of the aquatic environment. ECAO had overall responsibility to prepare the Human Health Effects Assessment Chapters and CAG was responsible for the carcinogen sections of the 65 Ambient Water Quality Criteria Documents (AWQCD) which were required under the Consent Decree (Environmental Defense Fund vs. Train). With the assistance of scientists from academic institutions, the private sector and government, ECAO developed guidelines for deriving ambient water quality criteria and applied these guidelines to the available data on the 129 compounds included in the 65 documents. Of the 129 priority pollutants for which criteria were eventually recommended, 43 were derived from carcinogenicity data, 29 from toxicity data, and 23 from organoleptic data. For 6 of the 129 pollutants no criteria were recommended. For some pollutants criteria were derived based on carcinogenic or organoleptic effects; toxic effect-based protective levels were also calculated for comparison.

The purpose of this paper is to present the approach that has been taken when confronted with promotion and/or cocarcinogenic data in assessing human health risk, and to raise questions so that improvements in the methods for assessing health risk from promoters and cocarcinogens will be developed. It is necessary to generate data that not only explain the mechanism of action of these agents but also to provide a satisfactory data base for quantitative risk assessment.

Ambient Water Quality Criteria

The development of the methodology employed to derive EPA's Ambient Water Quality Criteria has been discussed previously in detail (*11-13*). The following discussion is a concise review of the salient features of this methodology.

Ambient water quality criteria were derived from data on three possible types of biological endpoints: carcinogenic, toxic (i.e., all adverse effects other than cancer), and organoleptic effects. Carcinogenic response is regarded as a nonthreshold phenomenon. Therefore, "safe" or "no-effect" levels for carcinogens cannot be established because any dose must be assumed to elicit a finite response. Toxic and organoleptic effects are regarded as threshold phenomena. Therefore "safe" levels can be established.

After a review concluded that a compound had the potential to cause cancer in humans and data existed to permit the derivation of a criterion, the water concentration associated with a lifetime carcinogenic risk of 10^{-5} was estimated. The data used for quantitative estimates were of two types: (a) lifetime animal bioassays, and (b) human epidemiologic studies where excess cancer risk had been associated with exposure to the agent.

The method of risk assessment for a potential human carcinogen is not a clear-cut process. Several biologically plausible mathematical models have been used in the attempt to assess the risk. However, until the mechanism of carcinogenesis is firmly established and universally accepted, no single model can be identified which would interpret the true molecular aspect of carcinogenesis. Considering these uncertainties, a linear multistage model was chosen to assess the risk of carcinogenic substances in ambient water from data found in animal studies. The justification for the choice of this model and its formulation are discussed in detail elsewhere (*13*). Briefly, the multistage model (*14*) is based on the assumption that neoplastic transformation of a cell occurs after it has encountered heritable changes. Utilization of this model for estimating risk from carcinogenic pollutants in water is justified by the following characteristics:

- Carcinogens are or can be metabolized to electrophiles that react with DNA of the cell resulting in DNA damage, misrepair or incomplete repair.
- Many carcinogens are mutagens which can be detected by short-term tests, such as *Salmonella* plate incorporation assay.
- Carcinogenesis is an irreversible self-replicating process.
- Carcinogenesis is a multistage process. The simplest biological counterpart is the two-stage initiator-promoter mechanism of carcinogenesis.
- Mortality rates for several forms of cancer in the adult population increase as the fifth or sixth power of age, indicating cancer develops by a multistage process.

If human epidemiologic data and sufficiently valid exposure information are available for the compound, the data are analyzed by an alternate procedure to give an estimate of the linear dependence of cancer rates based upon the calculated lifetime average dose. If the epidemiology data show no carcinogenic effect when positive animal evidence is available, it is assumed that a risk exists but is smaller than could have been observed in the epidemiologic study. An upper limit of the cancer incidence is then calculated, assuming that the true incidence is just below the level of detection in the cohort studies. With this approach, the response is measured in terms of excess risk of the exposed cohort of individuals compared to the control group. In analyzing the data, it is assumed that the excess

risk is proportional to the lifetime average exposure and that it is the same for all ages (*15*).

Both of these procedures yield slopes termed $q_1^*(A)$ or B_H, for animal and human data respectively. Since $q_1^*(A)$ is derived from animal studies, it must be adjusted to yield an equivalent human slope, $q_1^*(H)$, by the following equation:

$$q_1^*(H) = \frac{[q_1^*(A)]}{(l_e/L_e)(L_e/L)^3}\left(\frac{70\text{ kg}}{w}\right)^{1/3}$$

where $q_1^*(A)$ = the upper 95% estimate of the linear component of the slope (potency factor) estimated from all the animal data, in $(\text{mg/kg/day})^{-1}$; l_e = the length of exposure; L_e = the length of the experiment; L = the lifespan of the animal; and w = average weight of the animal (in kg). The $(L_e/L)^3$ factor accounts for the increase in tumor incidence in time during a chronic study. For example, if a study lasted only one-half the normal lifespan of the animal, then the lifetime incidence is expected to be $(2)^3 = 8$ times as high as the incidence at the end of that study. Therefore, q_1^* is 8 times as large as the value calculated from the incidence at time L_e. Higher values of $q_1^*(H)$ are associated with lower, more restrictive, ambient water criteria. The rationale for the use of this factor is documented elsewhere (*13,15*). The cube root of the body weight ratios is a further refinement of the $q_1^*(A)$ potency factor, in that it represents an equivalent dose among species (*16*).

After the slopes describing carcinogenic potency in humans have been calculated, the intake I associated with a specific risk (usually 10^{-5} or 1 in 100,000) over a human lifetime is determined:

$$I(\text{mg/day}) = \frac{70\text{ kg}(10^{-5})}{[q_1^*(H)][\text{mg/kg/day})^{-1}]} = \frac{70\text{ kg}(10^{-5})}{B_H(\text{mg/kg/day})^{-1}}$$

The ambient water quality criterion (AWQC) is then calculated as follows:

$$C(\text{mg/L}) = \frac{I(\text{mg/day})}{(2\text{ L/d}) + \{[0.0065\text{ kg/day}][\text{BCF(L/kg)}]\}}$$

For this calculation, the average weight of a man is assumed to be 70 kg. The assumed average daily consumption of water and fish for a 70 kg man is 2 L and 0.0065 kg, respectively. BCF is the bioconcentration factor of the chemical (in L/kg).

For toxic compounds not manifesting any apparent carcinogenicity the threshold assumption was used in deriving a criterion. This assumption is based on the premise that a physiological reserve exists within the organism which must be depleted before clinical disease ensues. In developing guidelines for deriving criteria based on noncarcinogenic responses, five types of response levels are considered:

- NOEL: No Observed Effect Level
- NOAEL: No Observed Adverse Effect Level
- LOEL: Lowest Observed Effect Level
- LOAEL: Lowest Observed Adverse Effect Level
- FEL: Frank Effect Level

Adverse effects are defined as those which result in functional impairment and/or pathological lesions which may affect the performance of the whole organism, or which reduced an organism's ability to respond to an additional challenge. Frank effects are defined as overt or gross adverse effects (severe convulsions, lethality, etc.).

These concepts are illustrated in Figure 1 modified from dose-response curves proposed elsewhere (*17*). They have received much attention because they represent landmarks which help to define the threshold region in specific experiments. Thus, if an experiment yields a NOEL, a NOAEL, a LOAEL and an FEL in relatively close spaced doses, the threshold region has been relatively well defined. Such data are very useful for the purpose of deriving a criterion. On the other hand, a clearly

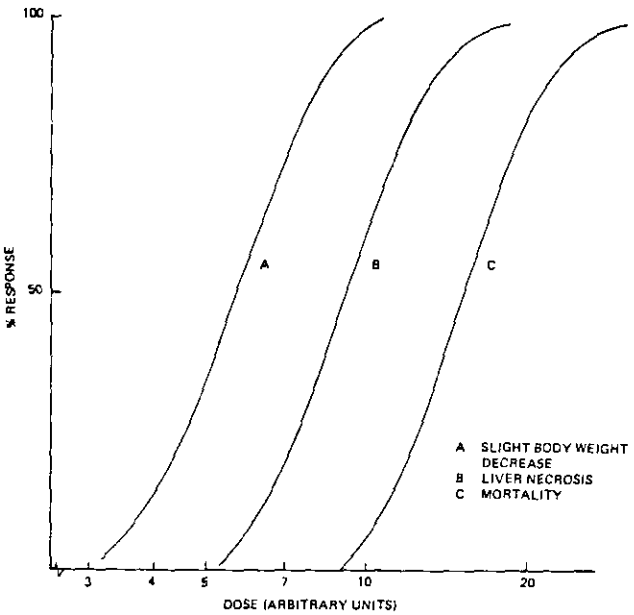

FIGURE 1. Response levels considered in defining threshold regions in toxicity experiments. Doses associated with these levels are as follows: 3-NOEL, NOAEL; 4-LOEL, NOAEL; 5-NOAEL (highest); 7-LOAEL; 10-FEL; 20-FEL. Modified from dose-response curves proposed by Norberg and Norseth (*17*).

defined FEL has little utility in establishing criteria when it stands alone, because such a level gives no indication how far removed it is from the threshold region. Similarly, a free-standing NOEL has little utility, because there is no indication of its proximity to the threshold region.

Organoleptic criteria define concentrations of materials which impart undesirable taste and/or odor to water, are not based on toxicologic information and have no direct relationship to potential adverse human health effects. Since organoleptic and human health effects criteria are based on different endpoints, a distinction was made between these two sets of information. In a number of cases, two approaches were used to derive criteria levels based on available toxicity and organoleptic data. Where sufficient data were not available to estimate a level which would protect against the potential toxicity, no criterion was derived.

In 1978-1979, when the guidelines were prepared, it became apparent that satisfactory methods had not been developed for either an accurate identification or usage of promotion/cocarcinogenic data in quantitative risk assessment. Moreover, the data on promoters or cocarcinogens did not permit a quantitative estimation of health risks incurred by this type of biological phenomenon. Therefore, in light of these issues, some of the pollutants in the 65 ambient water quality criteria documents with promotional activities (Table 1) were assigned criteria based on their carcinogenic properties using the modified multistage model. On the other hand, some criteria for these chemicals were derived on toxicity or organoleptic data because a sufficient data base for carcinogenicity was not available or other factors (e.g., route of exposure, essentiality, nutritional status of exposed individuals) played a role in the review committee's judgment. In none of these cases were promotion or cocarcinogenic data factored in developing the criteria (Table 2).

A few of these priority pollutants on which ambient water quality criteria were developed have been reported to be promoters and/or cocarcinogens. For example, TCDD, a carcinogen, appears also to be a promoter in hepatocarcinogenesis and a cocarcinogen in the development of sarcoma. Similarly, phenol, 2-chlorophenol, 2,4-dichlorophenol, fluoranthene, DDT, dieldrin, beryllium, nickel, cadmium

Table 1. The 65 consent decree water criteria documents.

Acenaphthene	Diphenylhydrazine
Acrolein	Endosulfan
Acrylonitrile	Endrin
Aldrin/dieldrin[a]	Ethylbenzene
Antimony	Fluoranthene[a]
Arsenic	Haloethers
Asbestos	*Halomethanes*
Benzene	Heptachlor
Benzidine	Hexachlorobutadiene (HCBD)
Beryllium[a]	Hexachlorocyclohexane
Cadmium (*in vitro* system)[a]	Hexachlorocyclopentadiene
Carbon tetrachloride	Isophorone
Chlordane	Lead
Chlorinated benzenes	*Mercury*
Chlorinated ethanes	Naphthalene
Chlorinated naphthalene	Nickel (*in vitro* system)[a]
Chlorinated phenols (3-chlorophenol)[a]	Nitrobenzene
Chloroalkyl ethers	Nitrophenols
Chloroform	Nitrosamines
2-Chlorophenol	PAHs
Chromium (in vitro system)[a]	PCBs
Copper	Pentachlorophenol
Cyanide	Phenol[a]
DDT[a]	Phthalate esters
Dichlorobenzene	Selenium
Dichlorobenzidine	Silver
Dichloroethylenes	Tetrachloroethylene
2,4-*Dichlorophenol*[a]	*Thallium*
Dichloropropanes/enes	Toluene
2,4-Dimethylphenol	Toxaphene
2,4-Dinitrotoluene	Trichloroethylenes
Dioxins (TCDD)[a]	Vinyl chloride
	Zinc

[a] Promoters and/or cocarcinogens

Table 2. Ambient Water Quality Criteria for priority pollutants with reported promotion/cocarcinogenic activities.

Priority pollutant	Criterion data base	AWQC criterion, μg/L
Beryllium[a]	Carcinogenic	6.8×10^{-2}
Cadmium[b]	Toxic	10
3-Chlorophenol[c]	Organoleptic	0.10
Chromium[b]	Toxic	50
DDT[a]	Carcinogenic	2.4×10^{-4}
2,4-Dichlorophenol[c]	Toxic	3.1×10^{3}
	Organoleptic	0.3
Dieldrin[a]	Carcinogenic	7.1×10^{-4}
Fluoranthene[a,c]	Toxic	42
Nickel[b]	Toxic	630
Phenol[c]	Toxic	3.5×10^{3}
	Organoleptic	3.0×10^{2}
TCDD[a,c]	Carcinogenic	2.1×10^{-9}

[a] Cocarcinogen.
[b] Promoter *in vitro* system.
[c] Promoter.

and chromium appear to have promoting/cocarcinogenic activities in various experimental conditions. Due to lack of any data indicating the potency of promoting or cocarcinogenic activities, these biological responses could not be used for human health risk assessment in developing their criteria. Consequently, the quantitative data base on other biological responses to these chemicals are utilized in developing ambient water quality criteria.

Examples of Data on Priority Pollutants

TCDD

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a highly toxic and stable compound. It has been demonstrated to produce adverse effects after acute, subchronic and chronic exposure in animals and man. The carcinogenic potential of TCDD has been established by feeding studies in rodents (*18-21*). The animal bioassay data in combination with the case-control studies suggest that TCDD is a potential human carcinogen (*22-31*).

Recently, TCDD has been shown to promote hepatocarcinogenesis (*32*) as well as to act as a cocarcinogen in the development of sarcoma (*33-35*). For example, the DBA/2N mouse strain, which responds only weakly to the sarcomatogenic action of 3-methylcholanthrene, becomes highly susceptible after treatment with TCDD (*32*). In two inbred strains of mice, C57BL/6Cum and DBA/2Cum, the administration of TCDD simultaneously with 3-methylcholanthrene appears to enhance the sarcomatogenic response (*34*). These observations suggest that TCDD acts as a cocarcinogen possibly by acting as an inducer of aryl hydrocarbon hydroxylase at the site of inoculation. Similarly, female Charles River rats exhibited marked increases in hepatic enzyme altered foci at TCDD doses of 0.14 and 1.4 μg/kg SC (one every 2 weeks for 7 months), given after partial hepatectomy and initiation with diethylnitrosamine (10 mg/kg). Hepatocellular carcinomas were observed at the higher TCDD dose; but no significant effects were seen without prior initiation (*32*). This observation suggests that TCDD is a potent promoter for hepatocarcinogenesis. Similar promoting action in the development of fibrosarcoma of the integumentary system was also observed in female (but not male) Swiss-Webster mice initiated with dimethylbenzanthracene (50 μg) and exposed dermally to 5 ng of TCDD, 3 days/week for 104 weeks (*35*).

Because TCDD is a carcinogen, the recommended AWQC for TCDD were based on carcinogenic data. The levels which result in incremental increase of human lifetime cancer risk due to exposure of TCDD through ingestion of contaminated water and contaminated aquatic organisms of 10^{-5}, 10^{-6}, and 10^{-7} were estimated to be 2.1×10^{-9} μg/L, 2.1×10^{-10} μg/L and 2.1×10^{-11} μg/L, respectively.

Phenol

Phenol has been reported to have tumor-promoting activity in several strains of mice when applied repeatedly to the shaved skin after initiation with known carcinogens. The tumor-promoting activity is highest at dose levels of phenol which have some sclerosing activity, but it also occurs in sensitive strains at concentrations which do not produce obvious skin damage.

The tumor-promoting activity of phenolic compounds has been tested in various strains of mice (*36*). Mice exposed to a single dose of the initiator DMBA by skin painting were given repeated der-

mal applications of selected phenols. In one experiment in this series mice specially inbred for sensitivity to develop tumors received a single application of 75 μg DMBA to the shaved skin. This was followed 1 week later by twice-weekly dermal applications of 2.5 mg phenol (as a 10% solution in benzene) for 42 consecutive weeks. The mice subjected to the skin application of phenol exhibited severe skin damage, decreased body weight and increased mortality. After 13 weeks, 22 of 23 mice had developed papillomas, and 73% had developed carcinomas. The skin painting with phenol was continued until the 72nd week, at which time one fibrosarcoma was diagnosed. It is worth mentioning here that these effects can also be due to benzene, a leukemogenic agent, which has been classified as a promoter (*37*). "S" strain albino mice demonstrated strong tumor-promoting activity after initiation with 0.3 mg DMBA followed by repeated skin applications of 20% phenol, and a moderate promoting effect with 5% phenol (*38*). Dermally applied phenol (3 mg/mouse, 3 times/week) has been found to have only slight promoting activity in ICR/Ha Swiss mice after initiation with BaP (approximate 0.05% solution) (*39*).

For comparison purposes, two approaches were used to derive criterion levels for phenol. Based on available toxicity data, the derived level was 3.5 mg/L. By using available organoleptic data, however, for controlling undesirable taste and odor qualities of ambient water, the estimated level was 0.3 mg/L.

3-Chlorophenol

3-Chlorophenol has promoting action when applied to the skin of mice in a series of experiments testing the tumor promoting action of substituted phenols (*36*). A 20% solution of 3-chlorophenol in benzene increased the number of papillomas following initiation by DMBA. If skin papillomas are considered in this format (i.e., in relation to carcinogenicity) then 3-chlorophenol exhibited a promoting action. However, due to the lack of any methodology for developing criteria based on promotion action, the criteria for 3-chlorophenol was derived based on available organoleptic data; the estimated level was 0.1 μg/L.

2-4-Dichlorophenol

Similarly, in the same series of experiments, 2-4-dichlorophenol was found to have promotion action on papillomas of the skin following initiation by DMBA (*36*). Based on available toxicity and organoleptic data, the AWQC for 2,4-dichlorophenol were estimated to be 3.1 mg/L and 0.3 μg/L, respectively.

Fluoranthene

Fluoranthene is a very weak tumor promoter on mouse skin in comparison to the action of classical tumor promoting chemicals such as phorbol myristate acetate (PMA) (the active component of croton oil) (*39*). However, a remarkable aspect of the biological activity of fluoranthene is its potency as a cocarcinogen. Two carefully conducted studies have shown that fluoranthene acts as a cocarcinogen for mouse skin cancer when applied with small quantities of benzo(a)pyrene (*39,40*).

Based on the use of chronic mouse toxicity data, the ambient water quality criterion for fluoranthene was estimated to be 42 μg/L.

DDT

The liver tumorigenesis of DDT has been demonstrated in mice (*41-45*) and in rats (*46,47*). There is no epidemiological evidence relating to the carcinogenicity of DDT. However, some investigators have detected DDT residues in cancer patients (*48, 49*) and in some cases in cancerous tissue (*50*). These observations, however, do not necessarily indicate that DDT is carcinogenic in humans.

Cocarcinogenic activities of DDT have been demonstrated by coadministration of DDT with 2-acetylaminofluorene (2-AAF) which enhanced the incidence of liver tumors in rats (*51*).

Considering all the available data, the ambient water quality criterion for DDT was derived from carcinogenic response in mice and the criterion associated with a human lifetime cancer risk of 10^{-5} was determined to be 0.24 ng/L.

Dieldrin

Chronic ingestion of dieldrin, an environmental and metabolic by-product of aldrin, a carcinogen, produced liver tumors in several strains of mice (*45,52*). These studies strongly suggest that dieldrin may pose a carcinogenic risk to man. Cocarcinogenic activities of dieldrin with DDT have also been demonstrated in mice (*45*). In light of the carcinogenic data in animals, the ambient water quality criterion for dieldrin was determined to be 0.71 ng/L in order to maintain the additional lifetime human cancer risk below 10^{-5}.

Beryllium

The high frequency of osteosarcomas in rabbits induced by intravenous injection of beryllium (*53*) and of reticulum cell sarcomas in rats by oral ingestion of beryllium (*54*), the positive results from mutagenic assays (*55*), and the suggestive human epide-

miologic data (*56,57*) indicate that beryllium-laden water poses a carcinogenic risk to man.

Data from a dietary study (*58*) was used to estimate the criterion associated with a lifetime human cancer risk of 10^{-5}. The resulting ambient water criterion was 68 ng/L. Regarding cocarcinogenicity, it has been demonstrated that beryllium oxide can potentiate the carcinogenicity of 3-methylcholanthrene (*59*).

Other Metal Salts

Recently, it has been demonstrated in an *in vitro* system with hamster embryo cells that certain metal salts have a promotion-like effect similar to that obtained with the tumor promoter TPA (12-O-tetradecanoyl phorbol-13-acetate) (*60*). These results indicated that nickel sulfate, cadmium acetate and sodium chromate act as promoters in the transformation of cells initiated by BaP. In ambient water quality criteria derivation, these metals have been treated in the following way.

Nickel. Although epidemiological data from occupational exposure to nickel compounds indicate carcinogenic potential through inhalation, there is no evidence for carcinogenicity of nickel compounds after exposure from contaminated water. Accordingly, for the protection of human health, the criterion for nickel was derived from the toxic properties of its salts ingested through contaminated water and aquatic organisms. The criterion was determined to be 630 μg/L.

Cadmium. The human evidence for the carcinogenicity of cadmium is weak because it is based on very small populations of workers and is accompanied by no clear-cut positive animals studies by the oral route. Accordingly, the criterion for cadmium was based on established toxic effects (i.e., emphysema and renal tubular proteinuria). The recommended ambient water quality criterion for cadmium was 10 μg/L to protect against these toxic effects.

Chromium. Evidence suggests that inhaled hexavalent chromium is a human carcinogen. However, the oral carcinogenicity of either hexavalent or trivalent chromium has not been demonstrated. Accordingly, the ambient water quality criterion for chromium was based on its toxic properties and was determined to be 50 μg/L.

Future Regulatory Considerations

Because some of these pollutants with promotion/cocarcinogenic activities are present in environmental mixtures together with other carcinogens, they may present an additional risk to the exposed population. Yet, because of the uncertainties as to the degree of the promotional/cocarcinogenic activity of these chemicals, the degree of added risk cannot be easily determined on the basis of present scientific knowledge. Due to the close association between some of the promoters/cocarcinogens and chemicals which are known carcinogens (initiators), it would seem prudent to temporarily limit the level of such pollutants in drinking water to the same concentration as "complete" carcinogens using the "linearized" multistage model. This approach can be revised if a sufficient data base for a different approach becomes available.

Given the complexities of promotion/cocarcinogenicity, it is not surprising that a definitive approach has not been recommended as yet for incorporating these concepts into a risk assessment methodology. An efficient promoter might test also as a weak or moderate "complete carcinogen" in a normal bioassay for carcinogenicity, thus presenting a dilemma in the risk assessment procedure. Consideration may have to be given to apply different extrapolation models to the two different types of response. To further clarify this issue, it has been recommended that an attempt be made to evaluate the potencies of promoters provided that such data are available (*61*). This is certainly a worthy approach and appears to be the path that some researchers are following. To increase, however, the size and quality of the data base from which correlations can be made and principles identified, it also seems desirable to develop more efficient screening tests for promoters.

Nonetheless, even if tumor promoters and cocarcinogens could be readily identified through screening tests or whole animal bioassays, problems would still remain in attempting to quantitatively apply such data to human risk assessment. In principle, some of these problems are the same as those already faced in developing a risk assessment approach for "complete carcinogens": the selection of appropriate or most defensible models for high-to-low dose and experimental animal-to-human extrapolation as well as a method for choosing the types of experimental data to use in the extrapolation (e.g., periods of exposure and observation) of lifetime risks. However, data on tumor promoters and cocarcinogens present an additional set of concerns similar to those which must be faced when dealing with mixtures of toxic agents. Specifically,

several major conceptual questions must be addressed before a satisfactory regulatory approach can be developed:

- How specific and consistent are initiator-promoter interactions? Does the promoting efficiency of a compound vary with initiating agents and, if so, does this variation follow a consistent or predictable pattern?
- How does exposure to multiple promoting agents affect the promoting efficiency of the individual promoters? If additivity is a reasonable assumption, which type of additivity might be expected based on what we know about the mechanism of promotion?
- How does promoting efficiency vary with the duration of exposure to the initiator and the promoter?
- Is there any validity in using promotion data from one route of administration to predict promoting activity from another route of exposure?

All of the above questions may apply equally to cocarcinogens and the answers may or may not be the same as those for promoters. Perhaps a more fundamental question would be: What is the most appropriate method for measuring promoting efficiency as a meaningful toxicologic parameter analogous to potency?

The National Academy of Sciences, in its recent review (*62*) on approaches to multiple chemical exposures, did not address the problems associated with promotion or cocarcinogenicity although it did outline approaches for dealing with mixtures of "complete" carcinogens. Dose-response equations based on Michaelis-Menton kinetics for cancer risk assessment have been proposed (*63*), and it may be possible to use this general approach to describe the effects of promoters or cocarcinogens. Similarly, biometricians may be able to construct modifications of other dose-response models to describe the effects of promoters or cocarcinogens on apparent carcinogenic potency. However, the meaningfulness and validity of any mathematic model will depend not only on how well it fits dose-response data but also on how well the mathematic constructs used to formulate the model reflect an understanding of the biologic basis of promotion and cocarcinogenicity. Whether our current understanding of these phenomena is sufficient to recommend a specific risk assessment approach is perhaps the most basic question of all. The EPA's Office of Health and Environmental Assessment is currently examining this issue internally using a review committee composed of in-house, academnic and industrial scientists. Various alternative approaches are being tested for dealing with nongenotoxic carcinogens with and without promotional or cocarcinogenic activity.

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